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Review Article

Review and comparison between the Wells–Riley and dose-response approaches to risk assessment of infectious respiratory diseases

Abstract Infection risk assessment is very useful in understanding the transmission dynamics of infectious diseases and in predicting the risk of these diseases to the public. Quantitative infection risk assessment can provide quantitative analysis of disease transmission and the effectiveness of infection control measures. The Wells–Riley model has been extensively used for quantitative infection risk assessment of respiratory infectious diseases in indoor premises. Some newer studies have also proposed the use of dose-response models for such purpose. This study reviews and compares these two approaches to infection risk assessment of respiratory infectious diseases. The Wells–Riley model allows quick assessment and does not require interspecies extrapolation of infectivity. Dose-response models can consider other disease transmission routes in addition to airborne route and can calculate the infectious source strength of an outbreak in terms of the quantity of the pathogen rather than a hypothetical unit. Spatial distribution of airborne pathogens is one of the most important factors in infection risk assessment of respiratory disease. Respiratory deposition of aerosol induces heterogeneous infectivity of intake pathogens and randomness on the intake dose, which are not being well accounted for in current risk models. Some suggestions for further development of the risk assessment models are proposed.

G. N. Sze To, C. Y. H. Chao

Department of Mechanical Engineering, The Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong

Key words: Infectious respiratory disease; Infection risk assessment; Outbreak investigation; Wells–Riley; Dose-response; Ventilation.

C. Y. H. Chao
Department of Mechanical Engineering
The Hong Kong University of Science and Technology
Clear Water Bay, Hong Kong
China
Tel.: +852 2358 7210
Fax: +852 2358 1543
e-mail: meyhchao@ust.hk

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Practical Implications
This review article summarizes the strengths and limitations of the Wells–Riley and the dose-response models for risk assessment of respiratory diseases. Even with many efforts by various investigators to develop and modify the risk assessment models, some limitations still persist. This review serves as a reference for further development of infection risk assessment models of respiratory diseases. The Wells–Riley model and dose-response model offer specific advantages. Risk assessors can select the approach that is suitable to their particular conditions to perform risk assessment.

Introduction

Quantitative infection risk assessment can serve as a useful tool in epidemic modeling, parametric studies on disease transmission and evaluating the effectiveness of infection control measures. It describes the infection risk of an individual or a population to an infectious disease quantitatively. Infection risk is expressed by a probability of infection between 0 and 1. By comparing infection risks, the influence of different environmental factors on disease transmission and the effectiveness of different infection control measures can be evaluated. Quantitative infection risk assessment can also be used in epidemiological studies such as outbreak investigations. Currently, there are two approaches to quantitative infection risk assessment of respiratory diseases, which can be transmitted via the airborne route: the Wells–Riley model and the dose-response model. The Wells–Riley equation was developed by Riley and colleagues in an epidemiological study on a measles outbreak (Riley et al., 1978). The equation is based on the concept of 'quantum of infection' as proposed by Wells (1955) and is therefore termed the Wells–Riley equation. The Wells–Riley model has been extensively used in analyzing ventilation strategy and its association to airborne infections in clinical environments (e.g., Escombe et al., 2007; Fennelly and Nardell, 1998; Nardell et al., 1991). The dose-response relationship is used to describe the effect on organisms from the exposure to different doses of chemicals, drugs,

radiation, bio-agents, or other stressors. Risk assessment models based on the dose-response relationship are called dose-response models. Originally, dose-response models were mainly used for risk assessment of hazardous chemicals. They were then developed for assessing the infection risk of foodborne and waterborne pathogens (Haas, 1983). Some newer studies have proposed to use dose-response models for assessing the infection risk of airborne-transmissible pathogens (e.g., Armstrong and Haas, 2007a; Nicas, 1996; Sze To et al., 2008). This article reviews the fundamental theories, formulations, model developments, and modifications of these two approaches. The strengths and limitations of the two approaches to infection risk assessment as well as to outbreak investigations are compared. Suggestions on further development of risk assessment models regarding their limitations are proposed.

Theory and formulation

Infection risk assessment models should be based on theories and mathematical equations that are biologically plausible or conformable to clinical or laboratorial evidences. Airborne respiratory pathogens can be generated from expiration actions and other activities that introduce pathogen-laden aerosols into the air. Pathogens released from the infectious source must reach the target infection site of the receptor to commence the infection. Even after the pathogen has successfully reached the target infection site, it must survive the immune defenses of the receptor organism to induce infection. A number of influencing factors affect this process and the outcome. They are listed in Table 1. These factors add complexities to the exposure and risk assessment of pathogenic microorganisms. Many of them are not well-understood, especially the pathogen–host interactions. As a result, statistics and probabilities are often employed to formulate quantitative infection risk assessment models.

Infection risk assessment consists of two components in general: the estimation of the intake dose of the infectious agent and the estimation of probability of infection under a given intake dose. The intake dose is the amount of the infectious agent reaching the target infection site. For airborne pathogens, estimation of intake dose requires knowledge of the exposure level to the infectious agent, pulmonary ventilation rate, exposure time interval, and the respiratory deposition of the infectious particles. Knowing the intake dose, the probability of infection can then be modeled by a mathematical function.

Infection risk assessment models can be divided into two categories: deterministic models and stochastic models. In deterministic models, each individual is hypothesized to have an inherent tolerance dose toward the infectious agent (Haas et al., 1999). When a receptor organism intakes a dose of pathogens equivalent to or exceeding his/her tolerance dose, infection will occur. Lower than this tolerance dose, the receptor organism will remain uninfected. Following this hypothesis, the model can determine whether an individual will be infected or not under a certain intake dose. On the contrary, stochastic models do not determine whether an individual will acquire infection or not under a certain intake dose. Instead, the models estimate the probability of acquiring the infection under the intake dose. More details on these two concepts will be discussed in further sections.

Some infection risk assessment models are classified as threshold models. When a population intakes a dose lower than the threshold dose, none of the individuals would acquire the infection, i.e., the infection risk would be zero. It should be noticed that the threshold dose is different from the tolerance dose in the deterministic models (Haas et al., 1999). Threshold dose is the minimum amount of pathogens required to initiate infection. When the intake dose exceeds the threshold dose, there will be a non-zero probability of infection. Tolerance dose is a deterministic indicator. When an individual receives an intake dose exceeding his/her tolerance dose, that individual will be infected. Examples and the assumptions of threshold models will be discussed in further sections.

Wells–Riley model: the quantum of infection and the Poisson probability distribution

Wells (1955) proposed a hypothetical infectious dose unit: the quantum of infection. A quantum is defined as the number of infectious airborne particles required to infect the person and may consist of one or more airborne particles. These particles are assumed to be randomly distributed throughout the air of confined spaces. Riley et al. (1978) considered the intake dose of airborne pathogens in terms of the number of quanta to evaluate the probability of escaping the infection as a modification of the Reed-Frost equation (Abbey, 1952). Together with the Poisson probability distribution describing the randomly distributed discrete infectious particles in the air, the Wells–Riley equation was derived as follows:

$$P_I = \frac{C}{S} = 1 - \exp\left(-\frac{Iqpt}{Q}\right) \quad (1)$$

where P_I is the probability of infection, C is the number of infection cases, S is the number of susceptibles, I is the number of infectors, p is the pulmonary ventilation rate of a person, q is the quanta generation rate, t is the exposure time interval, and Q is the room ventilation rate with

Table 1 Influencing factors on the airborne transmission of infectious disease

Factor	Description
Dispersion and distribution of airborne pathogens	How airborne pathogens disperse and distribute in the room air governs the exposure levels of the susceptible persons. The spatial distribution of airborne pathogens depends on the proximity to the infectious source, ventilation, and the geometry of the premises. The susceptible people would generally have different exposure levels and hence different degrees of infection risk. Assuming a uniform airborne pathogen distribution may cause significant error in the assessment (Noakes and Sleigh, 2008).
Ventilation strategy	Airborne pathogens can be dispersed to different locations by airflow. The ventilated airflow pattern has strong correlation to the spreading of airborne transmissible diseases (Li et al., 2007). The spatial distribution of infectious particles is very dependent on the airflow pattern. Infectious particles can be removed from the air by ventilation dilution, which depends on the ventilation rate.
Survival of pathogen	Pathogens may lose viability to cause infection by biological decay during the airborne stage, which is a sinking mechanism for respiratory pathogens. Airborne survival of pathogens often depends on the temperature and humidity (e.g., Schaffer et al., 1976).
Aerosol size	Expiratory aerosols and many other bioaerosols are polydispersed. The transport of aerosols depends on their aerodynamic size. Therefore, the dispersion of pathogen-laden aerosols is dependent on aerodynamic size and the exposure levels to these aerosols usually have spatial variations. The deposition loss of infectious particles also depends on their aerosol size (Chao et al., 2008).
Respiratory deposition	When airborne pathogens are inhaled by the receptor organism, not all but a fraction of the inhaled pathogen-laden aerosols may deposit on the target infection site in the respiratory tract. In addition, because of aerosol dynamics, the respiratory deposition of these aerosols is dependent on aerodynamic size. Because of the difference in respiratory deposition of aerosols with different sizes, the aerosols have different deposition fractions on different regions of the respiratory tract. For example, aerosols with sizes >6 μm are trapped increasingly on the upper respiratory tract, aerosols with sizes >20 μm generally do not deposited on the lower respiratory tract and those with sizes >10 μm generally do not reach the alveolar region (Hinds, 1999; Tellier, 2006).
Heterogeneous infectivity	Different regions of the respiratory tract may have different immune mechanisms. In other words, pathogens generally have different infectivity in different regions of the respiratory tract. For example, the ID_{50} of influenza virus is about two orders higher when the virus was introduced to the nasal cavity by intranasal drop than introduced to lower respiratory tract via aerosol inhalation (Alford et al., 1966; Douglas, 1975). As the respiratory deposition of aerosols depends on their sizes, the variation of pathogen infectivity when carried by infectious particles of different sizes was also observed, as shown by many experimental infection studies (e.g., Day and Berendt, 1972; Wells, 1955).
Air turbulence	As induced by air turbulence, airborne pathogens trend to be randomly distributed in air. Any estimated exposure level or intake dose would be an expected value rather than an exact value. Air turbulence also exists in respiratory tracts. Respiratory deposition fraction of aerosols is also an expected value rather than an exact value (Hinds, 1999). In other words, when the respiratory deposition fraction of aerosols with a particular size is β, each aerosol with this size would have a probability of successful deposition equal to β.
Pathogen–host interaction	When a host organism is exposed to the pathogen, whether the organism will be infected or not depending on the infectivity of the pathogen and the immune status of the host organism (Haas et al., 1999).
Control measures	Control measures such as respiratory protection, ultraviolet irradiation and particle filtration can reduce the exposure level of the susceptibles to airborne pathogens (Nazaroff et al., 1998).

clean air. The quanta generation rate, q, cannot be directly obtained, but estimated epidemiologically from an outbreak case where the attack rate of the disease during the outbreak is substituted into P_I. If the exposure time and ventilation rate are known, the quanta generation rate of the disease can be calculated from Equation 1.

The exponential term of any exponential equation should always be dimensionless. Following the definition by Wells (1955), a 'quantum' has a unit describing the number of infectious particles (or the number of airborne pathogens). Hence, the exponential term in Equation 1 is not dimensionless but has the unit of the number of infectious particles. Two different interpretations can be made on Equation 1:

- There is a unity infectivity term, with the unit of per infectious particle, in the exponential term.
- The infectivity term is implicitly included in the backward calculated quanta generation rate in the equation, i.e., q = infectivity term $\times$ number of quanta/unit time. The infectivity term may not be one.

Adding an infectivity term to the exponential term would make it dimensionless. The infectivity term describes the probability of each infectious particle to initiate the infection. It should be noticed that in the first interpretation, a unity infectivity term implies that the host is completely vulnerable to the pathogen. This will make the Wells–Riley equation only suitable for diseases such as tuberculosis, in which the definition of tuberculosis infection fulfills this condition (Huebner et al., 1993). A unity infectivity term also indicates that one quantum is equal to one infectious particle/pathogen and makes the model deterministic, because the individual is determined to be infected if his/her intake dose is equal to or greater than one pathogen. The first interpretation has also assumed that all inhaled infectious particles will successfully deposit on the target infection site in the respiratory tracts, which is not correct in general. Adopting the second interpretation, the equation is applicable to many diseases and it is a stochastic model. Respiratory deposition of infectious particles is implicitly considered in the calculated quanta generation rate. The calculated

quanta generation rate will be a combination of infectivity of the pathogen and the infectious source strength in the outbreak. When the Wells–Riley equation is used in risk assessment of pathogens with a threshold dose greater than one pathogen, it will provide more conservative assessment results at low intake doses. A more accurate approach is to use a multiple-hit exponential form (Haas, 1983; Nicas et al., 2005).

The Wells–Riley equation assumes well-mixed room air and a steady-state infectious particle concentration which varies with the ventilation rate. Although Riley et al. (1978) assumed that the biological decay of the airborne pathogen could be neglected, the biological decay of the pathogen during aerosolization and in the airborne state is implicitly considered in the calculated quanta generation rate. Many complexities in airborne disease transmission are also implicitly considered in the quanta generation rate.

The Wells–Riley equation provides a simple and quick assessment of the infection risk of airborne transmissible diseases. The basic reproduction number of the infection is calculated as C/I, which can be used to estimate the disease spreading risk in a large community. Many epidemic modeling studies have used the Wells–Riley equation as part of their mathematical models (e.g., Liao et al., 2005, 2008; Noakes et al., 2006).

Dose-response model: deterministic and stochastic models

Dose-response type infection risk assessment models require infectious dose data to construct the dose-response relationship. The term 'dose' refers to the quantity of the pathogen (WHO, 2003). Infectious dose data are obtained from experimental infections of test animals (or human subjects) by the pathogen. For example, when a group of test animals is exposed to a certain dose of pathogens and half of the test animals acquire the infection, this particular dose of pathogen is the 50% infectious dose. Interspecies extrapolation may be required when human infectious dose data are unavailable. There are both deterministic and stochastic types of dose-response models, which interpret the dose-response relationships in different ways.

Deterministic models are empirical models. Following the tolerance dose concept, infectious dose data are interpreted as the dose of pathogens that exceeds the tolerance dose of a portion of the population. For example, 50% infectious dose (ID_{50}) exceeds the tolerance dose of half of the susceptible population. When each person in a susceptible population intakes a dose of the pathogen equal to ID_{50}, half of the people will be infected. When the frequency distribution of this tolerance dose is known, the infection risk of a certain intake dose can be assessed. Figure 1 illustrates

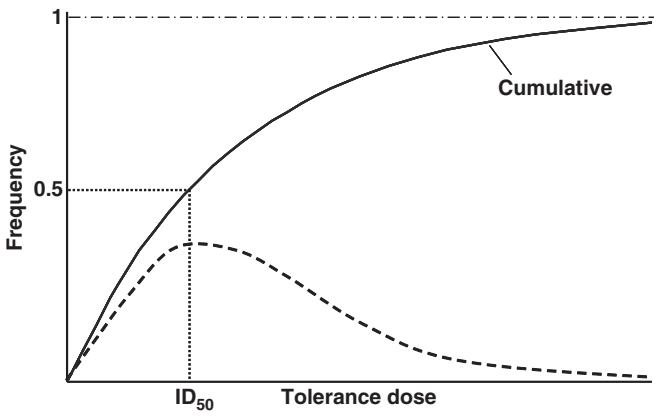

Fig. 1 An illustration of the frequency distribution of the tolerance dose

this idea. The cumulative curve describes the dose-response relationship. When each member of a susceptible population receives the same dose of pathogens, the infection risk is equal to the (cumulative) relative frequency of infection at this dose. The tolerance dose concept is biologically plausible in the sense that the immune status and the host's sensitivity to the pathogen vary between individuals as do their tolerance doses. In addition, some infection symptoms may only be observed after the host acquires a certain amount of pathogen in the body. However, it is not biologically plausible in the sense that the pathogens would inherently be assumed to be acting cooperatively, by which infection is the consequence of their joint action (Armitage et al., 1965; Haas, 1983). Some examples of deterministic dose-response models are shown in Table 2.

In contrast to the deterministic models, stochastic models are semi-empirical models. They assume that at any intake dose, the host will have a probability of getting infected. Generally, the greater the intake dose, the greater the probability of infection will be. In the stochastic single-hit models, the host must intake a dose containing at least one pathogen. At least one of the pathogens has to reach the infection site and survive until symptoms are provoked on the host. The models are formulated by solving these conditional probabilities. Some examples are shown in Table 2.

Stochastic dose-response models are more biologically plausible than the deterministic ones, as they are not based on the tolerance dose concept. In addition, some stochastic properties regarding the exposure and intake of the pathogens cannot be considered by the deterministic models. For example, the pathogens, as discrete matters, are randomly distributed in the suspension medium. The distribution of these pathogens in the air is also in a random manner as induced by air turbulence. Therefore, the estimated exposure level and intake dose of airborne pathogens are always expected values rather than exact values. Deterministic

Table 2 Examples of dose-response models

Model name	Description
Deterministic model	
Lognormal	Some experimental infection results suggested that the distribution of tolerance doses can be described lognormally (e.g., Nicas and Hubbard, 2002). Therefore, the lognormal model is one of the deterministic dose-response models: $P_I = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{Z} \exp\left(-\frac{x^2}{2}\right) dx;\ Z = \frac{\ln N - \mu}{\sigma}$ (2) where N is the intake dose, μ and σ are the mean and SD of natural logarithm of the tolerance dose, respectively. Equation 2 can be rewritten as the cumulative distribution function: $P_I = \frac{1}{2} + \frac{1}{2} erf\left(\frac{\ln N - \mu}{\sigma\sqrt{2}}\right)$ (3) where *erf* is the error function. μ and σ are determined by fitting the infectious dose data of the disease. The infectivity of the pathogen and the pathogen–host interactions are implicitly considered by the probability distribution of the tolerance doses, hence μ and σ.
Log-logistic, Weibull	These two deterministic models use different probability distributions in describing the distribution of the tolerance dose (Haas et al., 1999).
Stochastic model	
Exponential	The host organism must intake a dose containing at least one pathogen. At least one of the pathogens has to reach the infection site and survive until symptoms are provoked on the host. These conditions can be expressed by the following equation: $P_I = \sum_{j=1}^{\infty} P_1(j) P_2(k\|j)$ (4) where $P_1(j)$ is the probability of inhaling a number of j pathogens, $P_2(k \mid j)$ is the probability of a number of k pathogens from those j inhaled pathogens surviving inside the host to initiate the infection. The pathogens, as discrete matters, are distributed in a medium in a random manner described by the Poisson probability distribution. When the medium is aerosolized, the pathogen distribution in the aerosols and hence their distribution in the air also follows the Poisson probability distribution. Substituting the Poisson probability function into $P_1(j)$ in Equation 4 and using a constant, r, to express the probability of a pathogen surviving inside the host to initiate the infection, the probability of infection with an intake dose, N, is derived (Haas, 1983): $P_I = \sum_{k=1}^{\infty} \frac{(rN)^k \exp(-rN)}{k!}.$ (5) Simplifying the summation series, it becomes the exponential dose-response model: $P_I = 1 - \exp(-rN).$ (6) The infectivity of the pathogen and the pathogen–host interactions are implicitly considered by r.
Beta-Poisson	The variation of host sensitivity is not considered in the exponential dose-response model. To complement that, a distribution of the value of r rather than a fixed value can be considered. It is believed that the beta-distribution is the most plausible description for the r values (Moran, 1954). This results in the beta-Poisson model: $P_I = 1 - \frac{\exp(-N)\Gamma(\alpha+\beta)}{\Gamma(\beta)} \sum_{i=0}^{\infty} \left[\frac{\Gamma(\beta+i)}{\Gamma(\alpha+\beta+i)} \frac{N^i}{i!}\right]$ (7) where Γ is the Gamma function. The equation can be approximated as follows (Furumoto and Mickey, 1967): $P_I = 1 - \left(1 + \frac{N}{\beta}\right)^{-\alpha}.$ (8) The infectivity of the pathogen and the pathogen–host interactions are implicitly considered by r, α, and β in the equations. Similar to μ and σ in Equations 2 and 3, r in Equation 6 as well as α and β in Equations 7 and 8 are determined by fitting the infectious dose data of the disease[a,b]. The approximate form does not work well when β is small and/or N is large. In the example of Norwalk virus, the estimates are $\alpha = 0.040$ and $\beta = 0.055$ (Teunis et al., 2008). If $N = 25$ virus, the exact equation predicts a 50% chance of infection, whereas the approximation only predicts a 22% chance of infection.

[a]When calculating the fitting parameters, whether or not the respiratory deposition of pathogen-laden aerosols should be considered is dependent on the infectious dose data. If the infectious dose data refer to the inhaled dose, respiratory deposition of pathogen-laden aerosols can be implicitly considered by the fitting parameters. The intake dose would be: $N = pC_t$, where C_t is the total exposure concentration to viable pathogens. If the infectious dose data refer to the deposited dose of pathogen-laden aerosols on to the respiratory tract, the deposition fraction of pathogen-laden aerosols should be considered explicitly. The intake dose would be: $N = \beta pC_t$, where β is the deposition fraction of pathogen-laden aerosols onto the respiratory tract.
[b]Taking r in the exponential form as an example, with an ID_{50} data, r can be calculated by substituting 0.5 to P_I and the ID_{50} value into N in Equation 6, which equals to $-\ln 0.5/ID_{50}$.

models often regard the intake dose as an exact value and ignore this randomness, which may cause error in the assessment.

In practice, the model providing the best fit to the infectious dose data on the disease should be selected for infection risk assessment. The selection of the model will also depend on the availability of the infectious dose data. If there is only one available infectious dose value, only the exponential model can be used as the other models require at least two infectious dose values to calculate the fitting parameters.

Threshold models versus non-threshold models

Exponential dose-response model and the beta-Poisson model belong to the category of non-threshold models, as they assume that an infection could be initiated by a single pathogen reaching the infection site and

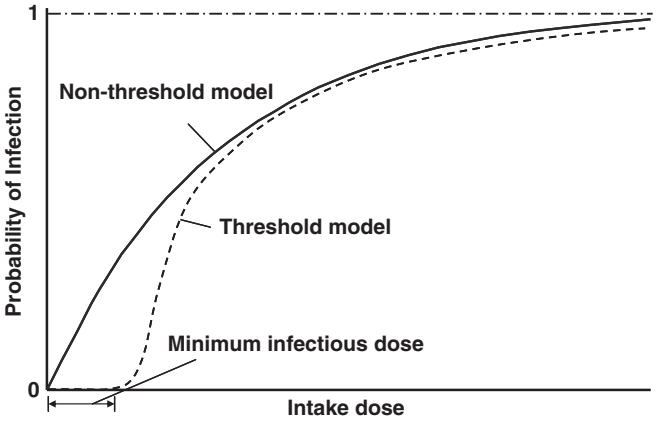

Fig. 2 An illustration of the difference between a non-threshold model and a threshold model

surviving in the host. In threshold models, infection risk is generally zero if the intake dose is lower than the threshold dose. Figure 2 illustrates the difference between threshold and non-threshold models. The threshold dose will be reflected in the distribution of the tolerance dose when deterministic model is used. For stochastic model, to incorporate the effect of the threshold dose, a multiple-hit model needs to be used (Nicas et al., 2005). A simple multiple-hit model can be obtained by modifying Equation 5 (Haas et al., 1999):

$$P_I = \sum_{k=k_{\min}}^{\infty} \frac{(rN)^k \exp(-rN)}{k!} \tag{9}$$

where $k_{\min}$ is the threshold dose. More complicated threshold models can be found in Haas et al. (1999).

Although the threshold dose concept is not the same as the tolerance dose concept, threshold models also inherently assume that the pathogens act cooperatively (Rubin, 1987). This assumption is not biologically plausible, as pathogen attacks on an organ or cell are spontaneous and independent actions and they do not have 'joint actions' or 'cooperative attacks'. In addition, after pathogens successfully attack the organ or cell, they may quickly replicate inside the host body and eventually reach a critical amount sufficient to provoke infection symptoms in the host. There is sufficient evidence to support the argument that only a single pathogen is required to commence infection of some diseases, including tuberculosis and smallpox (Nicas et al., 2004; Wells, 1955). However, some arguments suggest that threshold models do provide more accurate assessment results for some diseases, especially under low intake doses. Some experimental infection studies have observed threshold dose among the test animals (e.g., Cafruny and Hovinen, 1988; Dean et al., 2005). In such cases, the threshold models would provide a better fit to these infectious dose data.

The observation of a threshold dose may involve some complex biology. It could also be attributed to the limited number of the test animals when conducting experimental infection study. To obtain the dose-response relationship of a pathogen, different doses of the pathogen are given to different groups of test animals in experimental infection study. For instance, if each group consists of 10 test animals and the given dose has its true probability of infection to the test animals less than 0.05, it is most likely that no test animal in that group would be infected. If no test animal is infected under this given dose or other doses lower than this given dose, this given dose will be an observed threshold dose of the pathogen. With this limitation, a threshold dose may be observed even if the pathogen does not have such a threshold.

After all, the model providing the best fit to the infectious dose data of the pathogen should be used in the infection risk assessment.

Model development and modification

To complement some of the limitations and increase the feasibility of the infection risk assessment models, subsequent developments and modifications were performed by various researchers.

Wells–Riley model

Incorporating additional influencing factors. The original Wells–Riley model considered the ventilation rate as the only influencing factor to the infection risk. There are many other factors and control measures that can affect the infection risk. Use of a respirator will reduce the number of inhaled infectious particles. It is feasible to incorporate a parameter in the Wells–Riley equation indicating this reduction. The $Iqpt/Q$ term in Equation 1 is the intake dose with unit of quantum. The effect of respiratory protection can be considered by multiplying this term by a fraction (Fennelly and Nardell, 1998; Nazaroff et al., 1998; Nicas, 1996):

$$P_I = 1 - \exp\left(-R\frac{Iqpt}{Q}\right) \tag{10}$$

where R is the fraction of particle penetration of the respirator. It equals 1 when no respirator is used.

Particle filtration and air disinfection, such as ultraviolet irradiation, are additional airborne pathogen sink mechanisms other than ventilation removal. The effect of these control measures can also be incorporated into the Wells–Riley model (Fisk et al., 2005; Nazaroff et al., 1998):

$$P_I = 1 - \exp\left(-\frac{Iqpt}{Q + \lambda_{UV}V + Q_r\eta_r}\right) \tag{11}$$

where λ_{UV} is rate coefficient of inactivation by ultraviolet irradiation, V is the room volume, Q_{r} is the flow rate to the filter, and η_{r} is the filtration efficiency. Some

studies also suggested that the deposition loss of infectious particles and the viability loss of pathogens while airborne can also be considered by adding these sink terms in the denominator, similar to Equation 11 (Fisk et al., 2005; Franchimon et al., 2008):

$$P_I = 1 - \exp\left(-\frac{Iqpt}{Q + \lambda_V V + \lambda_{Dep} V}\right) \quad (12)$$

where λ_V is the rate coefficient of viability loss of the pathogen in the airborne state, λ_{Dep} is the rate deposition loss of the infectious particles. However, readers should be aware that when the quanta generation rate, q, is backward calculated from an outbreak case by Equation 1, removal by ventilation is implicitly assumed to be the sole sink mechanism for the airborne pathogen during that outbreak case. Therefore, the calculated q has already implicitly considered the deposition loss of infectious particles and the viability loss of pathogens in the airborne state of that outbreak case. If this quanta generation rate is used in Equation 12, the effects of these influencing factors would be considered twice and would lead to underestimation of the infection risk. To consider these two influencing factors using the Wells–Riley model, knowledge of the deposition and viability losses during the outbreak case is required. By substituting these two parameters into Equation 12, a quanta generation rate of the disease without implicit consideration of ventilation removal, deposition and viability losses as airborne pathogen sink mechanisms during the outbreak can be obtained. Risk assessors can then perform risk assessment with consideration of these influencing factors with Equation 12 using this quanta generation rate. Likewise, if the place of an outbreak case is equipped with ultraviolet irradiation or air filtration devices or the occupants have used respiratory protection, using Equation 1 to calculate the quanta generation rate during the outbreak will obtain a q implicitly considering these influencing factors. It is inappropriate to use such quanta generation rates for parametric studies of these factors. Risk assessors should either calculate the q using Equation 10 and/or Equation 11 or use a q calculated from another outbreak case that does not include the influence of these factors.

Allowance for non-steady-state and imperfect mixing. The assumption of a steady-state and well-mixed airborne pathogen concentration is one of the major limitations of the original Wells–Riley equation. Subsequent modifications were made to overcome this limitation. Gammaitoni and Nucci (1997a) described the changes in the quanta level in room air using a differential equation. By considering the time weighted average pathogen concentration in the room air instead of assuming the concentration has reached a steady-state, a risk assessment equation that incorporates non-steady-state condition was developed:

$$P_I = 1 - \exp\left(-\frac{pIq}{V}\frac{\Lambda t + e^{-\Lambda t} - 1}{\Lambda^2}\right) \quad (13)$$

where Λ is the air change rate or disinfection rate. Equation 13 still relies on the well-mixed assumption and adopting this equation will imply that the susceptible person or population is present in the premises starting from $t = 0$, or that the initial quanta concentration in the room air is 0. When this is not the case, the initial quanta concentration in the room air has to be considered (Gammaitoni and Nucci, 1997b):

$$P_I = 1 - \exp\left(-\frac{pIq}{V}\frac{\Lambda t + e^{-\Lambda t} - 1 - (\Lambda n_o/q)e^{-\Lambda t} + (\Lambda n_o/q)}{\Lambda^2}\right) \quad (14)$$

where n_o is the initial quanta level in the room air. Equation 13 can also be used to calculate the quanta generation rate from an outbreak, it would provide more accurate estimation than using Equation 1 in general, especially when the exposure time interval is short.

Rudnick and Milton (2003) have also proposed a modified Wells–Riley equation using the exhaled air volume fraction to estimate the number of quanta that the susceptible people are exposed to:

$$P_I = 1 - \exp\left(-\frac{\bar{f}Iqt}{\eta}\right) \quad (15)$$

where $\bar{f}$ is the average volume fraction of room air that is exhaled breath and η is the total number of people in the premises. In this equation, the exponential term is equal to the number of quanta inhaled by each susceptible person. The model estimates the pathogen concentration in room air indirectly. Investigators may need to monitor the carbon dioxide concentration in the room in order to estimate $\bar{f}$.

To obtain spatial variation of infection risk, some investigators used multiple box models or divided the premises into multiple zones (e.g., Ko et al., 2001, 2004), where the susceptibles may have different degrees of exposure in terms of quanta and thus different levels of infection risk. Rudnick and Milton (2003) developed Equation 15 to incorporate non-steady-state condition, but the model still adopts the

well-mixed assumption. However, with their proposed concept, the equation can also incorporate spatially distributed infection risk. When the amount of exhaled breath generated by the infectors and inhaled by a susceptible person in a particular spatial location is known, the susceptible person's exposure in terms of number of quanta and the infection risk can be estimated. This can be done by conducting tracer gas measurements. In such measurements, tracer gas is released from the locations of the infectors and the concentrations of the tracer gas at the locations of each susceptible person are then measured. The amount of exhaled breath inhaled by a susceptible person can be calculated by the measured concentrations and the released concentration. This parameter can also be obtained numerically by computational fluid dynamics (CFD). A numerical model of the premises is constructed. Gas surrogate is injected into the model at the locations of the infectors and its dispersion is simulated numerically. Spatial distribution of gas concentration is then obtained and the amount of exhaled breath inhaled by the susceptible person at different locations can be calculated. Some risk assessment studies have used these approaches to incorporate spatial variation into infection risk (e.g., Gao et al., 2008; Tung and Hu, 2008). These approaches can provide more realistic results, but they are more time-consuming than using the multiple box or multi-zone model.

Dose-response model

From foodborne to airborne. Dose-response assessment has a long history of use in analyzing the risk from chemical toxins. The concept has also been found to be feasible in assessing the risk of pathogenic microorganisms. The dose-response models have been widely adopted in quantitative risk assessment of infectious diseases transmitted via foodborne and waterborne routes and is recommended by the World Health Organization (2003). In waterborne and foodborne infections, as the contaminated water or food is consumed by ingestion, the pathogenic microorganism can directly reach the gastrointestinal region and hence the target site of infection. However, when assessing the risk of airborne infection, not all inhaled airborne pathogens will reach or be retained in the target infection site. Thus, the respiratory deposition of aerosols has to be considered. Exposure to airborne pathogens has to be assessed when estimating the intake dose. Exposure assessment is recognized by the National Academy of Sciences as one of the four components of the risk assessment paradigm for human health effects (National Academy of Sciences, 1983). Once the exposure level to the airborne pathogen is known, the intake dose can be estimated from the pulmonary ventilation rate and deposition fraction of the aerosols. The probability of infection can then be predicted using the dose-response equation. Therefore, it is critical to obtain a realistic exposure level in the susceptibles of airborne pathogens when adopting dose-response risk assessment models.

To the best of our knowledge, the first study using dose-response model in assessing airborne infection risk was performed by Nicas (1996) on tuberculosis:

$$P_I = 1 - \exp\left(-\frac{IGp\beta t}{Q}\right) \tag{16}$$

where G is the number of airborne tuberculosis bacilli released per infector per unit time and β is the deposition fraction of infectious particles in the alveolar region. Readers may notice that the equation is similar to the Wells–Riley equation with the quanta generation rate q replaced by $G\beta$ and it is also similar to the exponential dose-response equation with r equal to 1. The equation implicitly assumes that infection will occur if there is one bacillus successfully deposited on the alveolar region. Infectious particles are also assumed to have a Poisson distribution in the air. As a result, the probability of infection equals 0.63 when the exponential term equals 1. The first assumption delineates the host as completely vulnerable to the pathogen. Equation 16 is describing the probability of the susceptible person being exposed to the tuberculosis bacilli, i.e., getting a positive skin test. As having a positive skin test equates to tuberculosis infection (Huebner et al., 1993), Equation 16 is adequate for use to describe the probability of tuberculosis infection. For other diseases, the assumption that the host is completely vulnerable to the pathogen may not be appropriate. Nicas's work has shown the possibility of using the dose-response model in assessing the infection risk of disease transmitted via airborne route. Nicas and his colleagues modified the equation by expressing the infectious source strength term, G, as a multiple of cough frequency, pathogen concentration in respiratory fluid and the volume of expiratory droplets introduced into the air in a cough (Nicas et al., 2005). Other sinking mechanisms for the airborne pathogen were also considered in the modified equation with a formulation similar to Equation 11. These two dose-response models utilize the steady-state and well-mixed assumption on the airborne pathogen concentration.

The adequacy of using dose-response models in assessing airborne infection risk was further demonstrated by the work done by Armstrong and Haas on Legionnaires' disease. Because of the unavailability of human data on *Legionella*, interspecies extrapolation of infectious dose data from animal models was performed (Armstrong and Haas, 2007a). Risk extrapolation under low dose conditions was used to obtain

results with better relevance to the infectious dose data (Armstrong and Haas, 2007a). A near field–far field model was used to estimate the spatial variation of the exposure level (Armstrong and Haas, 2007b). The risk assessment results were validated by comparing the estimated risk and the reported attack rate from documented outbreak cases (Armstrong and Haas, 2007b, 2008). This series of studies has set a good example and put in place rigorous procedures in using dose-response models to assess airborne infection risk. The studies have also signified the potential of dose-response models in assessing the infection risk of exposure to pathogen-laden aerosols other than those generated by infected people.

Sze To et al. (2008) have developed an exposure assessment model that can incorporate the aerodynamic size-dependent factors regarding airborne pathogens:

$$E(x, t_o) = cp \int_0^{t_o} v(x, t) f(t) dt \tag{17}$$

where $E(x, t_o)$ is the exposure level of the pathogen at location x during the exposure time interval, t_o; c is the pathogen concentration in the respiratory fluid; $f(t)$ is the viability function of the virus in the aerosols; and $v(x, t)$ is the volume density of expiratory droplets at the location. $v(x, t)$ can be obtained by CFD modeling or by experiments (e.g., Wan et al., 2007). The spatial distribution of infectious particles can be reflected by this parameter. It is tedious and time-consuming to model every cough during the exposure time interval to obtain $v(x, t)$ at different locations. An alternative approach is to model the transport of the expiratory droplets after a single cough to obtain $v(x, t)$ at different locations and then to multiply the right-hand side of the equation by the total number of coughs during the exposure time interval. With other aerodynamic size-dependent factors considered, a stochastic non-threshold dose-response model for airborne pathogens can be formed:

$$P_I(x, t_o) = 1 - \exp\left(-\sum_{j=1}^{m} r_j \beta_j f_s t_o cp \int_0^{t_o} v(x, t)_j f(t) dt\right) \tag{18}$$

where m is the total number of size bins, $v(x, t)_j$ is the volume density of droplets of the j^{th} size bin and f_s is the cough frequency. As the infectivity (reflected in r) and β are aerosol size-dependent, $v(x, t)$ is thus split into different size bins. Generally, Equation 17 will provide more realistic exposure estimates, but it will be more time-consuming than obtaining the exposure level by the well-mixed assumption or other simple models. Equation 18 is especially suitable for parametric studies on the effect of environmental control, such as ventilation strategy or airflow pattern on the infection risk via airborne transmission.

Droplet and indirect contact transmission. Many respiratory infectious diseases can be transmitted via the airborne route and many of them can also be transmitted via droplet and indirect contact routes. It is also believed that the airborne mode may not be the major or only route of transmission for some respiratory diseases, such as SARS and influenza. Indirect contact transmission may be an important route of transmission for many respiratory pathogens (Beggs, 2003; Boone and Gerba, 2007). The result of risk assessment will be incomplete without considering these transmission routes. Dose-response models can assess the infection risk of these exposure pathways provided that the intake dose of the pathogen via these transmission routes can be estimated. Droplet transmission occurs when pathogens are carried in relatively large expiratory droplets. Unlike small expiratory aerosols, which can remain airborne for a long time and disperse over long distances, these expiratory aerosols can only travel short distances before settling. Under the definitions of the Centers for Disease Control and Prevention (2003), disease transmission via expiratory aerosols with sizes greater than 5 μm are in the droplet mode and with sizes smaller than or equal to 5 μm are in the airborne mode. However, studies found that expiratory droplet nuclei with sizes up to about 20 μm may also travel long distances similar to these aerosols with sizes smaller than or equal to 5 μm, depending on the airflow pattern and ventilation strategy (Chao and Wan, 2006; Wan and Chao, 2007). Therefore, a more rigorous approach to perform the dose-response infection risk assessment is not to distinguish into the airborne mode or the droplet mode, but directly split the exposure level into different aerodynamic size ranges for the infectious particles, such as Equation 18. Other dose-response models described in this article can also assess the infection risk via droplet transmission when the aerodynamic size-dependent factors are incorporated and an exposure assessment method that includes spatial variation of aerosol exposure levels is adopted.

Other than directly inhaling aerosolized respiratory pathogens, susceptibles may also be exposed to them via contacting surfaces contaminated by the deposited pathogens, as the conjunctiva and nasal mucous membrane can be portals of entry for some respiratory pathogens such as the measles and influenza viruses. When infectious particles are deposited on solid surfaces, these surfaces will become fomites. People contacting these contaminated surfaces may then deliver the pathogen to their eyes or nasal mucous membranes and may become infected. The first study assessing the infection risk via indirect contact transmission was performed by Nicas and Sun (2006).

A Markov chain model was used to estimate the intake dose of pathogens via indirect contact and also via other exposure pathways. When the intake dose is known, the infection risk can be assessed by the dose-response model. Their model assumes a steady-state pathogen load on contaminated surfaces, in which the rate of introducing the pathogens onto the surface equals the loss rate of the pathogen on the surface because of decay. This assumption is adequate for some pathogens with a fast or medium decay rate on the surface. Some pathogens will survive on solid surfaces for days or even weeks (Walther and Ewald, 2004) and at such a slow decay rate, the steady-state pathogen load will take a long time to reach. In this case, the error associated with this assumption will be large, especially for a short and medium exposure time interval. Nicas and Best (2008) have proposed an analytical model assessing the infection risk via indirect contact transmission by considering an average pathogen load on hand over the concerned exposure time interval.

Wan et al. (2009) have also developed a mathematical model describing the process of delivering pathogen to the mucous membranes via indirect contact transmission. The model also estimates the intake dose via indirect contact transmission. Their model can incorporate the non-steady-state pathogen load condition. It assumes that the decay of the pathogen on the contaminated surface is insignificant during the exposure time interval. Therefore, the equation is suitable for the case when the pathogen has a slow decay rate on the contaminated surface. In contrast, Nicas and Sun's model should be used when the pathogens have a fast or medium decay rate on the contaminated surface. With pathogens that can survive on inanimate surfaces for days or even weeks, the contaminated surfaces can serve as reservoirs for the pathogens up to weeks without effective disinfection. These fomites can impose potential infection risk to susceptible people for a long period of time, even after the source of the infectious particles has been removed. In this case, indirect contact transmission is the only exposure pathway to the susceptible people. Their model can also estimate the intake dose in this scenario.

Table 3 shows these models. With the estimated intake dose, the infection risk can be assessed using the dose-response model. To assess the combined infection risk via multiple exposure pathways, the simplest way is to sum up all the intake doses from different exposure pathways and then substitute into the dose-response model. However, as discussed in Table 1, pathogens have heterogeneous infectivity in different regions of the respiratory tract. Using a summed intake dose from different exposure pathways in dose-response assessment will only allow a single or a single set of fitting parameters that consider all the pathogens to have homogeneous infectivity. Essentially, pathogens encased in small aerosols will generally infect the lower respiratory tract, whereas pathogens encased in large aerosols will mainly infect the upper respiratory tract, and pathogens acquired via indirect contact will primarily infect the mucous membranes. Risk assessors should separate the intake dose for different exposure pathways and use different fitting parameters to obtain more realistic risk assessment results, unless the available infectious dose data are insufficient. To consider multiple intake doses from different exposure pathways, the dose-response equations would need to be reformulated. The exponential model is modified as follows:

$$P_I = 1 - \exp[-(r_1 N_1 + r_2 N_2 + \cdots + r_m N_m)] \qquad (21)$$

where r_1, r_2, r_m, N_1, N_2, and N_m stand for the fitting parameters and intake doses for the 1st, 2nd, and m^{th} exposure pathways, respectively. In the beta-Poisson model, the definite integral resulting in Equation 7 (Haas, 1983) is modified to:

$$P_I = \int_0^1 \int_0^1 \cdots \int_0^1 \{1 - \exp[-(r_1 N_1 + r_2 N_2 + \cdots + r_m N_m)]\} R(r_1) R(r_2) \cdots R(r_m) dr_1 dr_2 \cdots dr_m \qquad (22)$$

where R is the frequency distribution of the r value. For deterministic models, the probability of escaping infection from each exposure pathway has to be considered:

$$P_I = 1 - (1 - P_I, 1)\left(1 - P_{I,2}\right) \cdots \left(1 - P_{I,m}\right) \qquad (23)$$

where $P_{I,1}$, $P_{I,2}$, and $P_{I,m}$ are the infection risk via the 1st, 2nd, and m^{th} exposure pathways, respectively. The heterogeneous infectivity stochastic models can also be formulated using this 'escaping the infection' concept.

Limitations of the two approaches

Spatial heterogeneity of infection risk

Infectious particles become more diluted when they disperse farther from the source. The exposure level and hence the infection risk to respiratory pathogens are always expected to have spatial variation. As observed in many outbreaks associated with infectious respiratory diseases, the infection cases are often distributed with obvious proximity relationship to the index case (e.g., Gustafson et al., 1982; Marsden, 2003). Spatial distribution of the infectious particles is an important consideration in risk assessment of infectious respiratory diseases.

When the well-mixed assumption is adopted, the spatial variation of infectious particles distribution is

Table 3 Some models estimating intake dose via indirect contact of fomites

Model	References
$E_m = f_m c_m A_s \overline{C_{hand,t_o}} t_o \quad (19)$ $\overline{C_{hand,t_o}} = \frac{f_h c_h C_s}{(\varphi + f_h c_h + f_m c_m) t_o} \left[t_o + \frac{\exp(-(\varphi + f_h c_h + f_m c_m) t_o) - 1}{\varphi + f_h c_h + f_m c_m} \right]$ where E_m is the dose of pathogen delivered to the mucous membrane, c_h is the transfer efficiency of the pathogen from the surface to the hand after a contact, c_m is the transfer efficiency of the pathogen from the hand to the mucous membrane after a contact, f_h is the frequency of hand-to-contaminated surface contact, f_m is the frequency of hand-to-mucous membrane contact, A_s is the average contaminated surface area touched per hand contact, t_o is the concerned time interval, C_s is the pathogen load per area of the contaminated surface, and φ is the decay rate of pathogen on hand.	Nicas and Best (2008)
$E_m(n) = N_0 c_h c_m \frac{(1-c_h)^{\frac{f_h}{f_m}} - e^{-\frac{b}{f_m}}}{(1-c_h) - e^{-\frac{b}{f_h}}} A + \frac{f_s}{f_h} N_x c_m \left[\frac{1 - e^{-\frac{b}{f_m}}}{1 - e^{-\frac{b}{f_h}}} B - (1 - c_h) \frac{(1-c_h)^{\frac{f_h}{f_m}} - e^{-\frac{b}{f_m}}}{(1-c_h) - e^{-\frac{b}{f_h}}} A \right]$ $A = \frac{1-(1-c_h)^{\frac{f_h}{f_m} n}}{1-(1-c_h)^{\frac{f_h}{f_m}}} + c_h (1 - c_m) e^{-\frac{b}{f_m}} \frac{\left[1-(1-c_m)^n e^{-n\frac{b}{f_m}}\right]\left[1-(1-c_h)^{\frac{f_h}{f_m}}\right] - \left[1-(1-c_h)^{n\frac{f_h}{f_m}}\right]\left[1-(1-c_m)e^{-\frac{b}{f_m}}\right]}{\left[(1-c_h)^{\frac{f_h}{f_m}} - (1-c_m)e^{-\frac{b}{f_m}}\right]\left[1-(1-c_m)e^{-\frac{b}{f_m}}\right]\left[1-(1-c_h)^{\frac{f_h}{f_m}}\right]}$ $B = n + \frac{(n-1)c_h(1-c_m)e^{-\frac{b}{f_m}} - nc_h(1-c_m)^2 e^{-2\frac{b}{f_m}} + c_h(1-c_m)^{n+1} e^{-(n+1)\frac{b}{f_m}}}{\left[1-(1-c_m)e^{-\frac{b}{f_m}}\right]^2} \quad (20)$ where n is the number of hand-to-mucous membrane contact, N_0 is the pathogen load on the contaminated surface at time 0 and an additional amount of N_x pathogen is deposited on the contaminated surface after each cough, c_h in Equation 20 is the transfer efficiency of the pathogen from the surface to the hand factoring the ratio of the area of the fingerpad to the area of the contaminated surface and b is the decay rate of the pathogen on the hand.	Wan et al. (2009)

E_m is the intake dose of the pathogen via indirect contact transmission, probability of infection can be assessed by substituting this value into the dose-response models.

ignored and all the susceptible people have the same infection risk. This approach may cause underestimation of infection risk for the susceptible people in close proximity to the infectious source (Noakes and Sleigh, 2008). Newer models allow both approaches to consider the spatial variation of infection risk in the assessment. However, as the Wells–Riley models rely on backward calculated infectivity and infectious source strength (the quanta generation rate), there is currently no method to estimate the infectious source strength from an outbreak other than the well-mixed approach. When the infectious source strength term is backward calculated from an outbreak using the well-mixed assumption, the influences of the geometry of the premises, the airflow pattern, and the location of the infectious source on the spatial distribution of the infectious particles are implicitly considered in that infectious source strength. Using this infectious source strength in the risk assessments, even if the risk assessor has used a model that can incorporate spatial variation in exposure levels, these influencing factors cannot be explicitly adjusted and will become errors. Therefore, the errors associated with the well-mixed assumption still persist even though the risk assessor uses a modified Wells–Riley model that can consider spatial effects in the assessment. Dose-response models do not rely on backward calculation of infectivity and infectious source strength from outbreaks. Therefore, using the dose-response models that can consider spatial effects in the assessment can avoid those errors.

In epidemic modeling, where the spread of the disease in the community is concerned, it is difficult to specify the geometries, the airflow patterns and the locations of the infectious sources in every indoor premises, as these factors always vary from case to case. Therefore, adopting the well-mixed assumption is generally more reasonable than hypothesizing particular environments and scenarios in the modeling.

Randomness induced by air turbulence

As described in Table 1, air turbulence will induce randomness, which directly affects the intake dose of the airborne pathogen. The randomness induced by air turbulence consists of two components: the randomness in the pathogen distribution in air and the randomness of respiratory deposition of the inhaled pathogen. The former component can be described by Poisson probability as shown in some of the current risk models. For the latter component, if the respiratory deposition fraction is multiplied to the inhaled dose, the deposited dose will be the expected value and this randomness is not fully adjusted. When a person inhales an amount of N^* pathogens and the respiratory deposition fraction of the aerosols is β^*, an amount of $\beta^* N^*$ pathogens is most likely to be successfully deposited on his/her respiratory tract. However, it is also possible to have zero pathogen successfully deposited on his/her respiratory tract if the person has lottery-winning good luck or having all N^* pathogens successfully deposited on his/her respiratory tract if the person has very bad luck. Therefore, there should be a binomial probability distribution to describe this randomness. Taking the exponential

dose-response model as an example, the equation should be modified as:

$$P_I^* = \sum_{N=0}^{N^*} \binom{N^*}{N} (\beta^*)^N (1-\beta^*)^{N^*-N} P_I(N) \qquad (24)$$

where the first parenthesis is the binomial coefficient. Generally, this binomial distribution property is implicitly considered in the backward calculated quanta generation rate or in empirically obtained inhalation infectious dose data and thus the binomial probability of airborne pathogen deposition is reflected by these parameters. In a more rigorous sense, although the property has been implicitly considered by these parameters, it may not be fully adjusted, as binomial probabilities are different under different values of the expected intake dose. This is a limitation of both infection risk assessment approaches. In addition, respiratory deposition of aerosols is not yet well-understood. Scientists are still putting efforts on investigating the aerosol deposition in the respiratory tract and to characterize regional deposition (e.g., Choi and Kim, 2007; Park and Wexler, 2008).

Implicit errors

Many other factors are also implicitly considered by the backward calculated quanta generation rate or infectious dose data as previously discussed. This may cause errors in risk assessment results. Quanta generation rates and the fitting parameters of dose-response equation describe the infectivity of the pathogen. Pathogen–host interaction is implicitly considered by these parameters. Although the pathogen–host interaction has not been well-understood and quantified, it is reasonable to assume that the interaction between a particular species of pathogen and a particular species of host is rather consistent in different scenarios, while the variation in the individual host's immune status is either reflected statistically in the formulation of the model or is implicitly considered in the infectivity terms. However, other influencing factors that are being implicitly considered by the quanta generation rate or by the fitting parameters may have greater variation across different cases. The backward calculated quanta generation rate also does not distinguish whether the infection cases are caused by airborne, droplet, or indirect contact transmission or by a combination of all three, but it assumes that all infection cases are caused by airborne infection. This may also induce implicit error in the backward calculated quanta generation rate. Spatial heterogeneity, pathogen survivability, deposition loss of infectious particles, and other influencing factors are also implicitly considered in the backward calculated quanta generation rate. These factors always vary from case to case. The calculated quanta generation rate value will inherit all these influencing factors in that particular outbreak case. With so many influencing factors implicitly considered by a single parameter, the case-to-case variations and hence the implicit errors would be huge. As reviewed in one study, the quanta generation rate of tuberculosis calculated from different outbreaks ranged from 1.25 to 30,840 quanta/h (Beggs et al., 2003). Other than the variation of infectious source strengths, this huge variation is also likely to be attributed by these implicit errors. In dose-response models, as many of these influencing factors can be considered explicitly, there are fewer implicit errors in general.

Hypothetical infectious dose unit

The quanta generation rate describes the infectivity of the pathogen as well as the infectious source strength of the outbreak. This hypothetical infectious dose unit offers convenience for risk assessment but provides less information regarding the outbreak, as it cannot distinguish the pathogen emission rate from the pathogen's infectivity. When the quanta generation rates of two diseases are compared, epidemiologists cannot ascertain whether the one with a greater quanta generation rate is more infective than the other or that the infector has shed more pathogens during the outbreak than the other one. Infectivity of different pathogens can be easily compared by the infectious dose unit, in which the quantity of the pathogens can be directly compared. Dose-response model can also be used to calculate the infectious source strength of an outbreak. The infectious source strength can be expressed in terms of the quantity of the pathogen rather than a hypothetical unit. To demonstrate this idea, we selected an influenza outbreak during an air flight in Australia in 1999 (Marsden, 2003) as an example. As shown in Table 4, the calculated infectious source strength is 515 quanta/h or 2229.4 $TCID_{50}$/h. The total amount of influenza virus shed into the air during the outbreak is estimated as 7431.5 $TCID_{50}$. Knowing the amount of pathogens shed during an outbreak would provide further information to understand the transmission of disease.

Unavailability of infectious dose data

Dose-response models rely on infectious dose data to derive the dose-response relationship. A number of infectious dose values of a disease are usually needed to determine which dose-response equation best fits the infectious dose data for model selection. Dose-response models such as Equations 18, 21–23 also require a number of infectious dose values, for example, the infectious dose values of the pathogen suspended in aerosols of different sizes. Therefore, a rich infectious dose database is necessary. Infectious dose data are

Table 4 Calculation of infectious source strengths using the Wells–Riley and dose-response models

Parameters	Wells–Riley	Dose-response
Equation	$P_I = 1 - \exp\left(-\frac{Iqpt}{Q}\right)$	$P_I = 1 - \exp(-rN)$[a] where $N = IG_v\beta pt/Q$[b], G_v is the quantity of virus shed into the air per hour
P_I[c]	0.27	0.27
T	3.33 h	3.33 h
Q[d]	25 ACH	25 ACH
r	–	0.385[e]
Infectious source strength	q = 515 quanta/h	G_v = 2229.4 $TCID_{50}$/h[f]

An influenza outbreak during an air flight in Australia in 1999 (Marsden, 2003) was selected for the calculation. With a 3-h-and-20-min exposure time interval, 20 out of 74 susceptible persons were infected (27%).

[a]For comparison purposes, the exponential dose-response model was used.

[b]In addition, for comparison purposes, we assumed that the airborne mode was the only transmission route during the outbreak and ventilation dilution was the only sink for the airborne pathogen; both calculations adopted the steady-state and well-mixed assumption. β is assumed to be 0.6 (Alford et al., 1966).

[c]Attack rate of the disease during the outbreak was substituted into P_I in both equations.

[d]We assumed an air change rate of 25 during the outbreak which is the typical air change rate in commercial aircraft (Hunt and Space, 1995).

[e]Infectious dose data of influenza reported by Alford et al. (1966) was used (mean ID_{50} = 1.8 $TCID_{50}$). More details of r estimation can be seen in footnote b of Table 2.

[f]$TCID_{50}$ (50% tissue culture infectious dose) is a unit to quantify the amount of viable viruses.

often obtained by experimental infections but, for many pathogens, only animal data are available. Although interspecies extrapolation can be used in adopting these data to humans, using extrapolated animal data may still not fully adjust the difference of pathogen–host interactions between the two species. Risk assessors should be aware that the respiratory deposition of animals differs with that of humans (Asgharian et al., 1995) and this difference should also be considered when performing interspecies extrapolations. Some pathogens are too dangerous to be aerosolized to conduct infection experiments, such as the SARS coronavirus. Their infectious dose data are often unavailable.

In the Wells–Riley model, as the quanta generation rate is backward calculated from the outbreak case of the disease, the infectivity of the pathogen described in the quanta generation rate always refers to the infectivity of the pathogens in humans. Therefore, it does not require interspecies extrapolation of infectivity. These are great advantages over the dose-response models. Naturally, an outbreak case of the disease has to be available for obtaining quanta generation rate.

Suggestions for further developments

To minimize the uncertainty of respiratory deposition of airborne pathogens induced by air turbulence, the binomial probability property of respiratory deposition should be considered explicitly, for example, using Equation 24. The fitting parameters to be used should be calculated from the infectious dose data using this type of dose-response equation, so that the binomial probability property will not be implicitly considered in the calculated fitting parameters. If the infectious dose data are not obtained from the inhalation of aerosolized pathogens, for example, by intranasal inoculation, it would not contain the uncertainty of respiratory deposition. In this case, the fitting parameters should be calculated by a dose-response equation without considering the binomial probability distribution, such as Equation 6. Other influencing factors should also be considered explicitly with a similar procedure. This can reduce the implicit errors in the quanta generation rate or fitting parameters.

The current Wells–Riley model only models airborne transmission of respiratory infectious diseases. Aerodynamic size-dependent dispersion and deposition of the infectious particles cannot be considered. With advances in numerical modeling techniques, these shortcomings may be overcome. Newer CFD models allow using a gaseous surrogate to model the dispersion and deposition of polydispersed aerosols (e.g., Lai and Chen, 2007; Zhang and Chen, 2007). Combined with Rudnick and Milton's concept, the risk assessment model should be able to incorporate aerodynamic size-dependent dispersion and deposition loss, allowing assessment on the risk of droplet transmission route. When the amount of aerosols deposited on the contaminated surfaces is known, the exposure of the susceptible person to the pathogen via indirect contact transmission in terms of the number of quantum can be estimated by Equation 19 or 20. Therefore, the model should also be able to assess the risk of indirect contact transmission of the disease.

Conclusions

The Wells–Riley model implicitly considers many influencing factors, which provide convenience for risk assessment. With the backward calculated quanta generation rate, the Wells–Riley models can be used to perform risk assessment even when the infectious dose data of the pathogen are unavailable. Dose-response models are able to consider many influencing factors explicitly and therefore inherit less

implicit errors when performing risk assessment. Dose-response models can incorporate droplet and indirect contact transmission of respiratory infectious diseases, allowing them to provide a more complete risk assessment result than the current Wells–Riley models do. Dose-response models can also calculate the infectious source strength of an outbreak in terms of the quantity of pathogen rather than the number of quantum. This provides further information for epidemiologists in understanding disease transmission.

Spatial distribution of airborne pathogens is an important consideration, as it governs the exposure levels of the susceptible people. Respiratory deposition of aerosols also plays an important role in the intake and infection risk of respiratory pathogens. Heterogeneous infectivity is observed in airborne respiratory pathogens because of the difference in their carrier aerosol size and the subsequent respiratory deposition. This is also observed when the exposure to pathogen is carried out via different exposure pathways. As induced by air turbulence, there is a binomial probability property on the respiratory deposition of airborne pathogens, which is not being well adjusted in current risk models.

Newer numerical modeling techniques shed insights on overcoming the existing shortcomings of current risk models. Multidisciplinary knowledge is always necessary in the study of disease transmission and in formulating infection control strategies. With further developments in the two risk assessment approaches, we believe that both can serve as useful tools for understanding disease transmission mechanisms and developing infection control strategies.

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